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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,413	02/23/2004	Irwin Braude	99-005-D1-CO	1863

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,413	BRAUDE, IRWIN	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *2-5 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-9 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election **without** traverse of Compound 5 (page 16, lines 1-4) as the elected species in the reply filed on 11/1/2006 is acknowledged.

Claims 2-5 and 10-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/1/2006.

Status of the Claims

Claims 1-16 are currently pending and are the subject of this Office Action. Claims 2-5 and 10-13 are withdrawn from consideration as being drawn to non-elected subject matter. Claims 1, 6-9 and 14-16 are presently under examination. This is the first Office Action on the merits of the application.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-9 and 14-16 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

There is insufficient written description for the broad genus of compounds instantly claimed that would indicate that Applicant was in possession of the compounds encompassed by the formulas recited in the instant claims. As an example, the claims recite prodrugs, heteroaryl groups and heterocyclyl groups. There is insufficient written basis for these claim limitations.

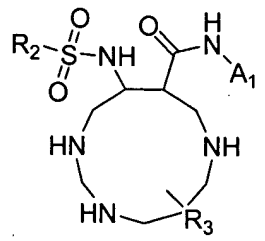
M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

Firstly, although the specification recites very generic synthetic methodologies for synthesizing the claimed compounds, the application only specifically describes compounds wherein A_2 is phenyl or naphthalene (*e.g.* Compounds 1-5). It is not at all evident that any other A_2 groups were actually synthesized or contemplated by the Applicant, aside from a cursory mention that A_2 can be any ringed structure consisting of aryl, heteroaryl, heterocyclyl or cycloalkyl.

Secondly, Applicant has not described the structural features of any prodrugs of the claimed compounds, nor is there is any description of any specific prodrugs of the claimed compounds in the specification.

Thirdly, the genus of "heteroaryl" encompasses hundreds, if not thousands, of possible structures. While Applicant has named several species of heteroaryl groups (*e.g.* thienyl, furanyl, thiazolyl, imidazolyl, (is)oxazolyl, pyridyl, pyrimidinyl, (iso)quinolinyl, napthyridinyl, benzimidazolyl, benzoxazolyl) at page 8, he has not described a sufficient number of species to convey possession of the entire genus of substituents encompassed by the claim limitation. Further, no examples are provided to demonstrate that Applicant was actually in possession of any heteroaryl substituted compounds at the time of the invention. The only examples provided in the specification are aryl-containing compounds (*i.e.* wherein A_2 is phenyl or naphthalene). No examples of any *hetero*aryl-containing compounds are described or contemplated in the specification.

Fourthly, the genus "heterocyclyl" encompasses any 5 to 11-member cyclic ring structure containing "one or more" ring heteroatoms selected from N, O and S. No specific examples are provided in the specification. It is not clear that applicant was in possession of any heterocyclyl groups as instantly claimed. For example, Applicant provides no direction or guidance on how the skilled artisan would synthesize the following 11-member heterocyclyl compound:



Thus, while the specification names a few heteroaryl groups, it does not name or contemplate any specific heterocyclyl groups, prodrugs, or cycloalkyls. Further, no specific compounds are named, synthesized or tested, aside from compounds wherein A_2 is phenyl or naphthalene. As such, the disclosure does not provided adequate written description for the

claimed genus of compounds that would indicate to the skilled artisan that Applicant was actually in possession of the claimed compounds at the time the invention was made.

Claims 1, 6-9 and 14-16 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the treatment of leiomyosarcoma/pelvic, does not reasonably provide enablement for the treatment of any and all tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of tumors comprising administering a very broad genus of compounds as recited in the instant claims. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Gura *et al.* (Science, 1997, 278:1041-1042) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Gura *et al.*, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraphs). It is noted that he pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 1) vary broadly, reciting the treatment of all tumors with a broad genus of compounds. Others, such as claims 14-16, are narrower, reciting specific tumors (*e.g.* sarcoma, carcinoma and mesothelioma). All, however, are extremely broad insofar as they disclose the general treatment of tumors with the same compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimes (dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans. The working examples are limited to: 1) the antitumor effects of one compound, on a very limited number of different tumors (*e.g.* leiomyosarcoma, fibrohistiocytic sarcoma, myxofibrosarcoma, gastrointestinal stromal tumor and ovarian) and 2) the inhibition of pelvic leiomyosarcoma tumors by five compounds. However, it is noted that only one example of a compound containing a naphthalene group as substituent A_2 is provided, and this is only demonstrated in a pelvic leiomyosarcoma tumor model (Table 3). All other tested compounds have a phenyl ring as substituent A_2. Thus, the applicant at best has provided specific direction or guidance only for the treatment of a single tumor type (pelvic leiomyosarcoma) with a specific compound (Compound 5). No reasonably specific guidance is provided concerning useful therapeutic protocols for any other tumors.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment for all tumors as inferred in the claims and contemplated by the specification.

It is evident from the disclosure that changing the A_2 substituent from a phenyl to naphthalene has a tremendous effect on the efficacy of the claimed compounds. For example,

Compound 5 (A_2 = naphthalene) is much less effective than Compounds 1-4 (A_2 = phenyl) (Table 3). Thus, the skilled artisan would not expect that any aryl, heteroaryl, heterocyclyl or cycloalkyl group could be used as the A_2 substituent and maintain efficacy in the treatment of tumors, even those for which some efficacy has been demonstrated.

Thus, it would take undue experimentation to determine exactly which compounds have efficacy in the treatment of tumors. Random synthesis and screening of thousands of possible compounds, although within the level of skill in the art, amounts to undue experimentation, with no reasonable expectation of success in actually discovering effective compounds. While the skilled artisan would expect that *some* compounds wherein A_2 is phenyl or naphthalene *may* show efficacy in treating *some* tumors, he/she would not reasonably expect that compounds wherein A_2 is something other than phenyl or naphthalene would demonstrate any specific efficacy. Further, Applicant has not provided any direction or guidance on which A_2 substituents might show efficacy, other than phenyl and naphthalene.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Allowable Subject Matter

Claims 1, 6-9 and 14-16 are free of the prior art of record and would be given favorable consideration for allowance if they were amended to overcome the outstanding 35 U.S.C. 112, 1st

Paragraph rejections, *e.g.* by limiting the claims to compounds wherein substituent A_2 is naphthalene and the tumors to be treated are leiomyosarcomas.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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AU 1614

January 24, 2007

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER